REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	May 31, 1988	Final January 1, 1987-December 31, 1987

4. TITLE AND SUBTITLE
OXYGEN TOXICITY RISK ASSESSMENT

5. FUNDING NUMBERS
N00014-87-C-0283

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
OFFICE OF NAVAL RESEARCH
DEPT. OF THE NAVY COE 1511:JRT
800 N. QUINAY ST.
ARLINGTON, VA 22217-5000

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
APPROVED FOR PUBLIC RELEASE: DISTRIBUTION IS UNLIMITED

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

Free 02 radicals, normal by-products of cellular respiration, cause cell damage and interfere with membrane transport. Defenses (e.g.,catalase & SOD) have evolved to deactivate free radicals under normoxic conditions. Under hyperoxic conditions, increased free radical production overwhelms defences,and risk of 02 toxicity exists by current theory. Assuming production proportional to cerebral 02 tension (the Hill equation defines Hb-02 dissociation) and constant deactivation, free radical concentration or "dose" may be calculated for any PI02 profile and related by a dose-response curve to 02 toxicity risk. The best agreement between predicted and observed risk was determined by the maximum likelihood method for 589 wet, working USN man-exposures (7 convulsions 20 definite symptoms). 02 toxicity risk was estimated for old and new USN exposure limits

This procedure could be developed for a diver worn computer to tract CNS 02 toxicity risk and to predict recovery during air breaks. Similar applications are possible for HBO therapy. With appropriate modification, the procedure can be adapted to analysis of pulmonary 02 toxicity data and prediction of toxicity risk.

14. SUBJECT TERMS	15. NUMBER OF PAGES
PULMONARY OXYGEN TOXICITY; CNS OXYGEN TOXICITY; STATISTICAL MODELING, DIVING	28
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLAS	UNCLAS	UNCLAS	UL

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. 239-18
298-102

[redacted]

Final Report

on

ONR Contract

N00014-87-C-0283

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OXYGEN TOXICITY RISK ASSESSMENT

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CONTENTS

Introduction

Oxygen toxicity is a consequence of breathing oxygen partial pressures greater than in atmospheric air. While oxygen itself is not toxic, the evidence indicates that toxic derivatives of oxygen are a by-product of cellular respiration. The production of toxic oxygen species increases as the tissue oxygen tension rises (Yusa et al. 1987), and toxicity probably occurs due to tissue damage or interference with normal function. The toxic oxygen species produced in normoxic conditions are deactivated, but under hyperoxic conditions they accumulate. The balance between production and removal of toxic species is well-suited to mathematical modelling and statistical analysis.

Gerschman (1964) was the first to suggest that oxygen toxicity might be caused by free radicals which are highly reactive and potentially damaging to cellular components. Although the valididty of this hypothesis remains to be proven absolutely, evidence has accumulated associating oxygen toxicity with increased generation rates of reactive oxygen species such as superoxide (O_2-), hydrogen peroxide (H_2O_2), singlet oxygen, and hydroxyl radicals (Freeman and Crapo 1981).

The principal reactions leading to these oxygen species are (Fridovich 1979; Freeman and Crapo 1981).

$$(O_2) + \text{electron} \rightarrow (O_2\text{-})$$

$$2\ (O_2\text{-}) + 2\ (H+) \xrightarrow{SOD} (H_2O_2) + (O_2)$$

$$2\ (H_2O_2) \xrightarrow{CAT} (O_2) + 2\ (H_20)$$

where the second and third reactions are catalyzed by superoxide dismutase (SOD) and catalase (CAT). If these reactions do not proceed to completion, hydroxyl radicals can also be formed.

The formation of a small number of reactive oxygen species is a normal by-product of cellular respiration (Fridovich 1979). Most of these are deactivated by SOD and CAT or may be scavenged by vitamins A, C, and E. Unscavenged oxygen species can damage cell membranes and intracellular enzymes by reacting with tissue proteins and lipids. This damage is repaired by cellular defense and biosynthetic mechanisms so that acute oxygen toxicity does not occur under normoxic conditions. If hyperoxia increases the production of reactive species beyond the deactivating capabilities of SOD and CAT and beyond the capacity of the reparative mechanisms, then cellular damage accumulates and eventually leads to symptoms of oxygen toxicity (Clark 1982; Fisher et al 1979).

PULMONARY OXYGEN TOXICITY

Clark-Lambertsen Free Radical Model

The UPTD concept introduced by Clark and Lambertsen (1970) to track the development of pulmonary oxygen toxicity may be interpreted as a balance between production and removal of a toxic substance. The UPTD concept was based upon a graphical analysis of decreases in vital capacity which occur during the inspiration of hyperoxic gas mixtures. These decreases were described by rectangular hyperbolas having the form

$$(PO_2 - 0.5 \text{ ATM})t = k$$

where 0.5 ATM is the estimated threshold PO_2 above which pulmonary toxicity begins to occur, and the constant k is an index of the decrease in vital capacity.

This relationship may be derived theoretically from a mass balance for a toxic substance (F). Consider a tissue in which F is produced at a rate proportional to the local PO_2 and removed at a constant rate. The mass balance for F gives

$$dF/dt = c_1 PO_2 - c_2$$

Integrating F with respect to time (t),

$$F(t) = F_o + (c_1 PO_2 - c_2)t \qquad (1)$$

where F_o is the initial concentration of F and c_1 and c_2 are constants. This can be re-arranged into the form given by Clark and Lambertsen (1970).

$$(PO_2 - c_2/c_1) = (F - F_o)/c_1 \qquad (2)$$

Neglecting the exponent of t, which Bardin and Lambertsen (1970) later raised to 1.2, the Pulmonary Toxicity Dose (PTD) is defined as

$$PTD = c_3 (PO_2 - c_2/c_1)t \qquad (3)$$

where $c_3 = 2$ and $c_2/c_1 = 0.5$ ATM.

Rearranging these terms gives the familiar expression

$$PTD = t(0.5/(PO_2-0.5))^{-1}$$

and the percent change in vital capacity (VC) is approximately

$$VC = - c_4 (PTD - c_5) \qquad (4)$$

where $c_4 = 0.01$ and $c_5 = 415$.

This formulation of the Clark-Lambertsen concept may be given the following interpretation. Under normoxic conditions, a diver does not have pulmonary oxygen toxicity and his vital capacity is unaffected. According to equation (1), all free radicals are removed and F = 0 since

$$c_1 \, PO_2 \leq c_2$$

Thus, the initial free radical concentration is zero or

$$F_o = 0$$

By combining equations (2) - (4) and eliminating redundant constants

$$Vc = - c_4 \, (F - c_5) \qquad (5)$$

Equations (1) and (5) define a model which can follow changes in vital capacity during any oxygen partial pressure profile. Where experimental measurements of vital capacity are availabe, moreover, the error between measured and estimated % VC change can be determined and the best values for the model parameters can be found by minimizing this error.

Vital Capacity Data

The Clark-Lambertsen model was applied to the vital capacity data compiled by Harabin et al (1986). All control measurements before the start of hyperoxic exposure were included in the data set giving 794 vital capacity measurements rather than the 440 studied by Harabin et al (1986). Data points for each subject were converted from liters to percent vital capacity change by dividing by the first control measurement for each subject.

Vital Capacity at Low PIO_2

The use of vital capacity as an index of pulmonary oxygen toxicity is frequently criticized because of variability in repeated measurements. This is reflected in Fig. 1 which is a frequency diagram of 312 vital capacity measurements made at PIO_2's of 0.21 to 0.5 ATM before exposure to higher PIO_2's. The percent change in vital capacity was tabulated over increments of 2%. The mean PIO_2 and % VC change of this distribution are 0.296 ATM and -1.11%. Thus, use of the first vital capacity measurement to define the normal vital capacity for each subject underestimated the mean by 1%.

Ninety-five percent of this distribution (the "95% VC Range") falls between % VC changes of -11 and +8%. This suggests that a vital capacity measurement must differ from the mean by approximately ±9% for there to be a 95% chance that the measurement is valid and not a statistical aberation.

Figure 2 subdivides the measurements from Fig. 1 into 3 smaller ranges as shown in Table 1.

Table 1. Percent change in vital capacity at PIO_2's of not more than 0.5 ATM

No. of Measurements	PO_2 Range (ATM)	Mean PO_2 (ATM)	Mean % VC Change	95% VC Range
74	0.21-0.23	0.214	-0.924	-13% to +7%
130	0.28-0.34	0.298	-1.117	- 9% to +5%
48	0.47-0.5	0.482	-2.263	-13% to +4%
312	0.21-0.5	0.296	-1.110	-11% to +8%

The number of measurements in the first three rows does not sum to the number in the fourth row to avoid the influence (should it exist) of 0.5 ATM PIO_2's on subsequent VC measurements at lower PIO_2's. The 95% VC Range varies from 14% to 20% for the three PIO_2 sub-ranges.

While there are no striking differences in the 3 distributions of Fig. 2, Fig. 3 shows a plot of the mean %VC change against the mean PIO_2 for each distribution and suggests a decrement in vital capacity with increasing PIO_2 at values of up to 0.5 ATM. It is commonly assumed that a PIO_2 of 0.5 ATM can be tolerated with no change in vital capacity, and this may be true for many people. Harabin et al (1986), however, demonstrated significant variation in individual response to elevated oxygen partial pressure, and susceptible individuals may be responsible for the decrements in Fig. 3.

Vital Capacity Data Analysis

The vital capacity data was analyzed by finding the best fit of free radical models (i.e., equation (1)) and vital capacity models (i.e., equation (5)) to the 794 data points. This fit was accomplished by finding the values of the model parameters (i.e., c_1, c_2, c_4, and c_5 in equations (1) and (5)) which minimized the sum of the squared errors (SSE) between the predictions of the model and the data. The minimization was accomplished by the incremental optimization procedure described in Vann (1987) with the addition of a variable step size for each undetermined parameter.

While many free radical and vital capacity models were evaluated, none (surprisingly) performed better than the simplest models discussed below. Besides the Clark-Lambertsen free radical model described earlier and designated FR(1), another free

radical model (FR(2)) assumed that free radical elimination had a term proportional to its own concentration or

$$dF/dt = c_1 PO_2 - (c_2 + c_3 F)$$

This equation has the solution,

$$F(t) = (F_o - c_4) e^{-c3t} + c_4$$

where

$$c_4 = (c_1 PO_2 - c_2)/c_3.$$

The vital capacity model of equation (5) was simplified to

$$VC = -F$$

in which each rectangular hyperbola defined by equation (1) corresponds to a different decrement in vital capacity. This is designated as vital capacity model VC(1).

Model VC(1) predicts that the vital capacity can decrease to less than -100%. As this is unrealistic, model VC(2) was defined in which the vital capacity has a minimum limiting value of -100%. Thus,

$$VC = -100 (1 - b_1^{-F}).$$

The free radical and vital capacity models are summarized in Table 2.

Table 2. Principal free radical and vital capacity models.

N	FR(N)-Free Radical Model	VC(N)-Vital Capacity Model
1	$dF/dt = c_1 PO_2 - c_2$ $F(t) = F_o + (c_1 PO_2 - c_2) t$	$VC = -F$
2	$dF/dt = c_1 PO_2 - (c_2 + c_3 F)$ $F(t) = (F_o - c_4) e^{-c3t} + c_4$ $c_4 = (c_1 PO_2 - c_2)/c_3$	$VC = -100 (1-b_1^{-F})$

For an analysis of vital capacity data, the PO_2 in the models of Table 2 is the alveolar value in the lungs. This value was defined as

$$PAO_2 = PIO_2 - PH_2O - PACO_2$$

where $PH_2O = 47$ torr and $PACO_2 = 40$ torr

$$PAO_2 = PIO_2 - 0.053 \text{ ATM}.$$

Model FR(1)-VC(1) is identical to models used by Harabin et al (1986). In their analysis, vital capacity measurements were treated as discrete points. In the analysis reported here, each vital capacity measurement depends upon the previous measurement. Thus, decreases in vital capacity develop and resolve continuously for individual subjects. The Harabin report analyzed 440 measurements while this report analyzed 794. These included all measurements made at POI_2's of 0.5 ATM or less.

Table 3. Results of dataset analysis with various models. Add 0.053 ATM to c_2/c_1 to arrive at the PIO_2 which can be tolerated indefinitely. More exact parameter values are given in Appendix A. The numbers in parentheses are from Harabin et al (1986).

	Free Radical Model & Constants	Vital Capacity Model & Constants	SSE	%VC Change	
				TT5	TT6
1	FR(1) c_1 = 0.011 c_2/c_1=0.5 ATM	VC(1)	145,179	-2.20 (-2.3)	-4.25 (-4.0)
2	FR(1) c_1=0.009 c_2/c_1=0.38 ATM	VC(1)	156,427	-1.95 (-2.0)	-3.79 (-3.0)
3	FR(1) c_1=0.0024 c_1/c_2=0.28 ATM	VC(1)	55,948	-0.56	-1.09
4	FR(1) c_1=0.021 c_2/c_1=0.41 ATM	VC(2) b_1 = 1.0055	31,538	-2.43	-4.66
5	FR(2) c_1=0.0092 c_2/c_1=0.17 ATM c_3=0.00031	VC(1)	37,214	-2.21	-4.23
6	FR(2) c_1=0.021 c_2/c_1=0.41 ATM c_3=-0.28×10^{-7}	VC(2) b_1=1.0055	31,518	-2.86	-5.05

Table 3 presents the model parameter values, Sum of Squared Errors (SSE), and predicted vital capacity changes for Oxygen Treatment Tables 5 and 6 (TT5 and TT6). Rows 1 and 2 of Table 3 use the "minimized" and "simplified" parameters from the Harabin analysis, and Row 3 presents the results for the same model optimized as model FR(1)-VC(1). There are large differences in SSE between the Harabin models (Rows 1 and 2) and the optimized model (Row 3) which is not unexpected given the different datasets and applications of the model. This points out the importance of the dataset in determining the behavior of a given model. Indeed, it might be said that a dataset is represented by the parameter values.

The % VC changes for TT5 and TT6 given in parentheses in Rows 1 and 2 are the values computed by Harabin et al (1986). In Row 3, the value of the oxygen asymptote (c_2/c_1 + 0.053) is 0.333 ATM, below the commonly used value of 0.5 ATM. The % VC changes for TT5 and TT6 are only half of those predicted in Rows 1 and 2.

Row 4 is the optimized model FR(1)-VC(2). Placing a limit on the vital capacity decrement substantially improves the SSE and increases the oxygen asymptote to 0.463 ATM. Row 5 is model FR(2)-VC(1). The SSE is improved over FR(1)-VC(1), but the oxygen asymptote is now 0.223 ATM which seems unreasonably low. Comparing FR(1)-VC(2) and FR(2)-VC(2) in Rows 4 and 6, there is little difference in SSE, and the value of c_3 is small. Thus, there appears to be little justification for using a model more complicated than the modified version of Clark-Lambertsen designated FR(1)-VC(2).

Among other models tested were sigmoidal vital capacity relationships, an $F*PO_2$ term in the free radical model, and a vital capacity model incorporating the time integral of F. None of these models performed as well as FR(1)-VC(2).

Recovery of Vital Capacity Decrements

One of the more interesting aspects of oxygen toxicity modelling is the recovery of vital capacity decrements upon return to near normoxic breathing gas. Figure 4 is the oxygen partial pressure profile described by Eckenhoff and Vann (1985) during decompression from a saturation dive which tested the development and recovery from pulmonary oxygen toxicity in 12 divers as indicated by changes in vital capacity. The vital capacity measurements were reported by Harabin et al (1986). Figure 5 is taken from Harabin's report and is a graphical representation of the % VC changes for all 12 divers.

Figure 6 is the prediction, using model FR(2)-VC(2) from Row 6 of Table 3, of the % vital capacity changes during the oxygen partial pressure profile of Fig. 4. The mean vital capacity

changes for the 12 divers from Fig. 5 are also shown in Fig. 6. The predicted and mean profiles agree quite well during the decrease in vital capacity while the PIO_2 is 1.05 ATM. There is essentially no change in predicted VC when the PIO_2 is 0.5 ATM, but the experimental mean may undergo a decrease indicating some recovery. The fluctuations during this period may reflect the individual variabiity which Harabin et al (1986) noted in their analysis. During the subsequent recovery phase, the predicted and mean values are in good agreement except for the final period in which predicted recovery is faster than the experimental mean.

It is also of interest to note that PIO_2 = 0.59 ATM in the 5 min air breaks during TT5 and TT6. Thus, these air breaks may provide no recovery from pulmonary toxicity.

CNS OXYGEN TOXICITY

Cerebral Oxygen Tension

The free radical models developed above also can be applied to an analysis of CNS toxicity data. In the case of CNS toxicity, the relevant tissue PO_2 is substantially lower in the brain than in the lungs for pulmonary toxicity. To find the lower PO_2 in the brain, the following procedure was adopted:

1. Determine the PAO_2 as described earlier:

$$PAO_2 = PIO_2 - 0.053 \text{ ATM}$$

2. Use the Hill equation to relate the PAO_2 to the oxygen content of arterial blood (CAO_2). The physically dissolved oxygen must be included. Thus

$$CaO_2 = \alpha O_2 * PAO_2 + C100/(1 + (a_1 P_aO_2)^{-a2})$$

where αO_2 = 0.023/ATM is the physical solubility of oxygen in blood,

C100 = 0.197 ml O_2/ml blood is the oxygen carrying capacity of saturated hemoglobin, and

a_1 = 24 and a_2 = 2 are constants to fit the Hill equation to the HbO_2 dissociation curve.

3. Use the Fick relationship to find the venous oxygen content (CvO_2) after assuming values for cerebral blood flow (Q) and cerebral oxygen consumption (m). Thus,

$$CvO_2 = CaO_2 - \frac{m}{Q}$$

where m and Q are assumed to be

$m = 3$ ml O_2/min/100 g tissue

$Q = 55$ ml/min/100 g tissue.

4. Use the relationship in Step 2 to find $Pv0_2$ from knowledge of $Cv0_2$. This relationship cannot be solved explicitly for $Pv0_2$ and must be solved numerically. Appendix B tabulates this solution which is available in the computer program as a look-up table. The depth in Appendix B is the water depth at which the diver is assumed to breathe 100% oxygen. The PIO_2, PAO_2, and PvO_2 are also given. It is assumed that the $Pv0_2$ is the relevant parameter for the development of CNS oxygen toxicity.

The numerical values assumed for the various constants in the procedure described above were allowed to vary as undertermined parameters when the models were fit to the data. Surprisingly, they had little influence on the final result.

CNS Oxygen Toxicity Data

The human CNS oxygen toxicity data used in the analysis was from U.S. Navy studies published by Lanphier (1954), Butler and Thalmann (1984; 1986), Piantadosi et al (1979), Schwartz (1984), and Butler (1986). Consistent with these reports and current NEDU practice, symptoms of CNS oxygen toxicity were defined as Probable, Definite, or Convulsions. The data was analyzed in 3 symptom categories:

1. Convulsions only (11 occurrences)

2. Convulsions and Definite Symptoms (44 occurrences)

3. Convulsions, Definite, and Probable Symptoms (81 occurrences)

The total number of man-exposures was 773.

Models and Analysis

Symptoms were treated as a binary variable: 0 when absent and 1 when present. This allowed the method of maximum likelihood to be used as described by Vann (1987) with a variable parameter step size introduced to accelerate convergence.

The models FR(1) and FR(2) were used to describe the kinetics of the toxic substance. Sigmoidal probability models were used to relate the free radical concentration (F) to the probability (P) of CNS toxicity symptoms. The most successful probability model, however, was similar to VC(2),

$$P(F) = 1 - b_1^{-F}.$$

Indeed, while the maximum log likelihoods were somewhat less for FR(2) and the sigmoidial probability models, some of the op-

timized parameters were found to have values of zero which rendered the models of no predictive use.

The most successful model was, again, the simplest: the modified Clark-Lambertsen FR(1) and the probability model given above. Appendix C presents parameter values for analysis of the 3 symptom categories.

Using the oxygen asymptote defined by c_1/c_2 and Appendix B, the following predictions are made for the depth on 100% oxygen at which a diver has zero risk of developing CNS toxicity:

Symptom Category	Max Safe O_2 Depth
1. Convulsions only	19 fsw
2. Conv. and Def. Sx.	20 fsw
3. Conv., Def., and Prob. Sx	16 fsw

Appendix C also gives the probability of symptoms for the old and new U.S. Navy oxygen exposure limits and the oxygen exposure times at 5 fsw depth increments for symptom probabilities of 0.01 to 0.08 in increments of 0.01. For the old and new exposure limits at 25 fsw, for example, the following probabilities were found:

	Sx Prob at 25 fsw for	
Symptom Category	75 min	240 min
1. Conv. only	0.008	0.025
2. Conv. & Def.	0.031	0.095
3. Conv., Def. & Prob	0.061	0.183

An example of the development and resolution of the probability of CNS toxicity symptoms is shown in Figs. 7 and 8. Figure 7 shows an oxygen dive profile with 120 min at 20 fsw, 15 min at 40 fsw, and 105 min at 20 fsw. Figure 8 shows the percent risk of convulsions or definite symptoms (Category 2). This risk increases slowly at 20 fsw to about 0.2%, rapidly at 40 fsw to about 4.1%, and slowly at 20 fsw to about 4.3%. Upon surfacing, the risk drops to 0% in 10 minutes.

CONCLUSIONS

It is evident that both pulmonary and CNS oxygen toxicity can be modelled with simple assumptions and these models fit to existing bodies of data. The human data currently available is

limited but allows preliminary estimates to be made. These should be considered relative estimates which can be used for planning future experiments and perhaps providing rough operational guidelines. With additional data and better models, improvements will probably follow. The methods also should be readily applicable to the analysis of animal experiments.

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FIGURE 1. Distribution of %vital capacity changes at PO2's of 0.5 ATM or less.

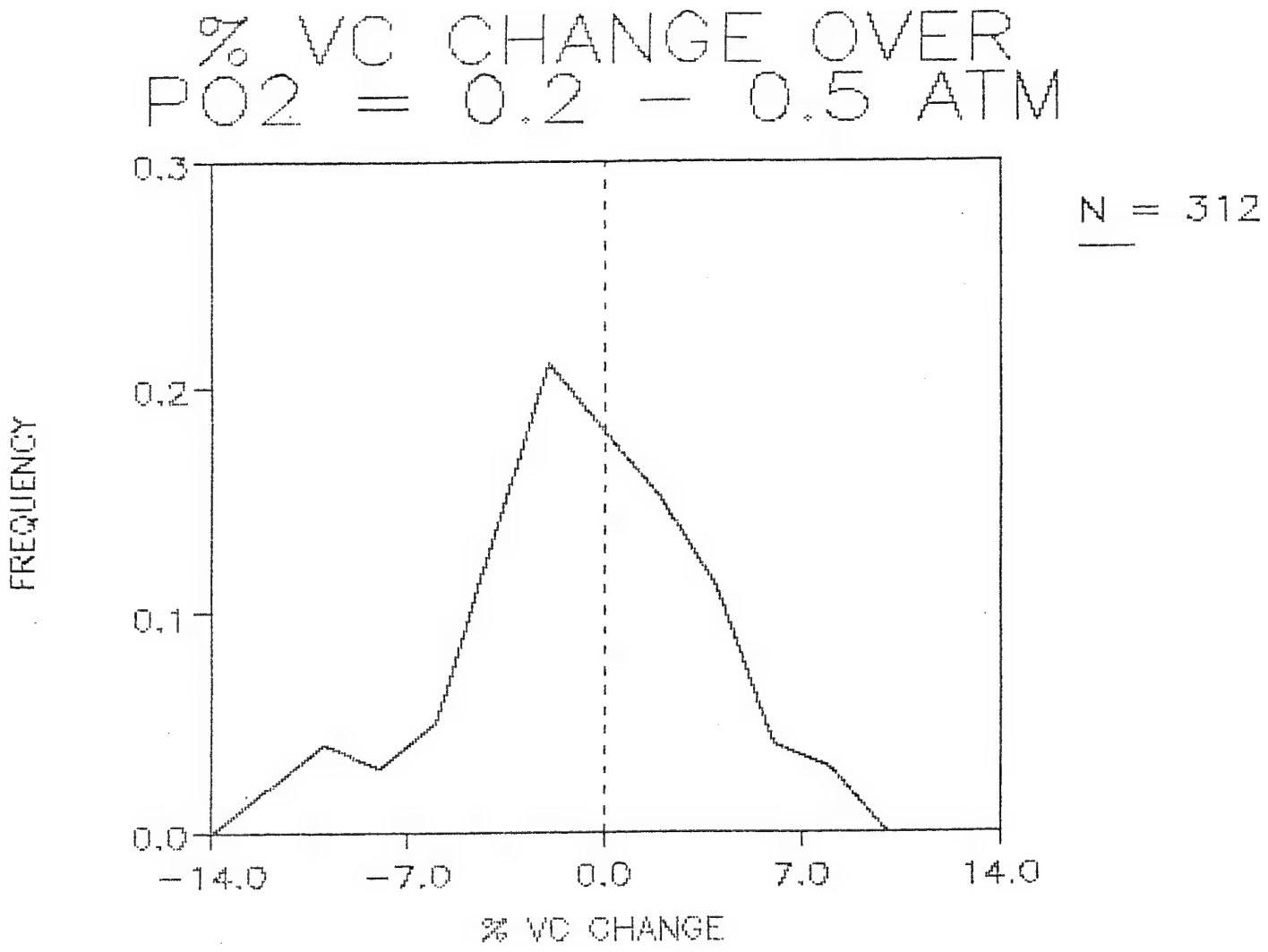


FIGURE 2. Distribution of % vital capacity changes over PO2 ranges of 0.21-0.23 ATM, 0.28-0.34 ATM, and 0.47-0.5 ATM.

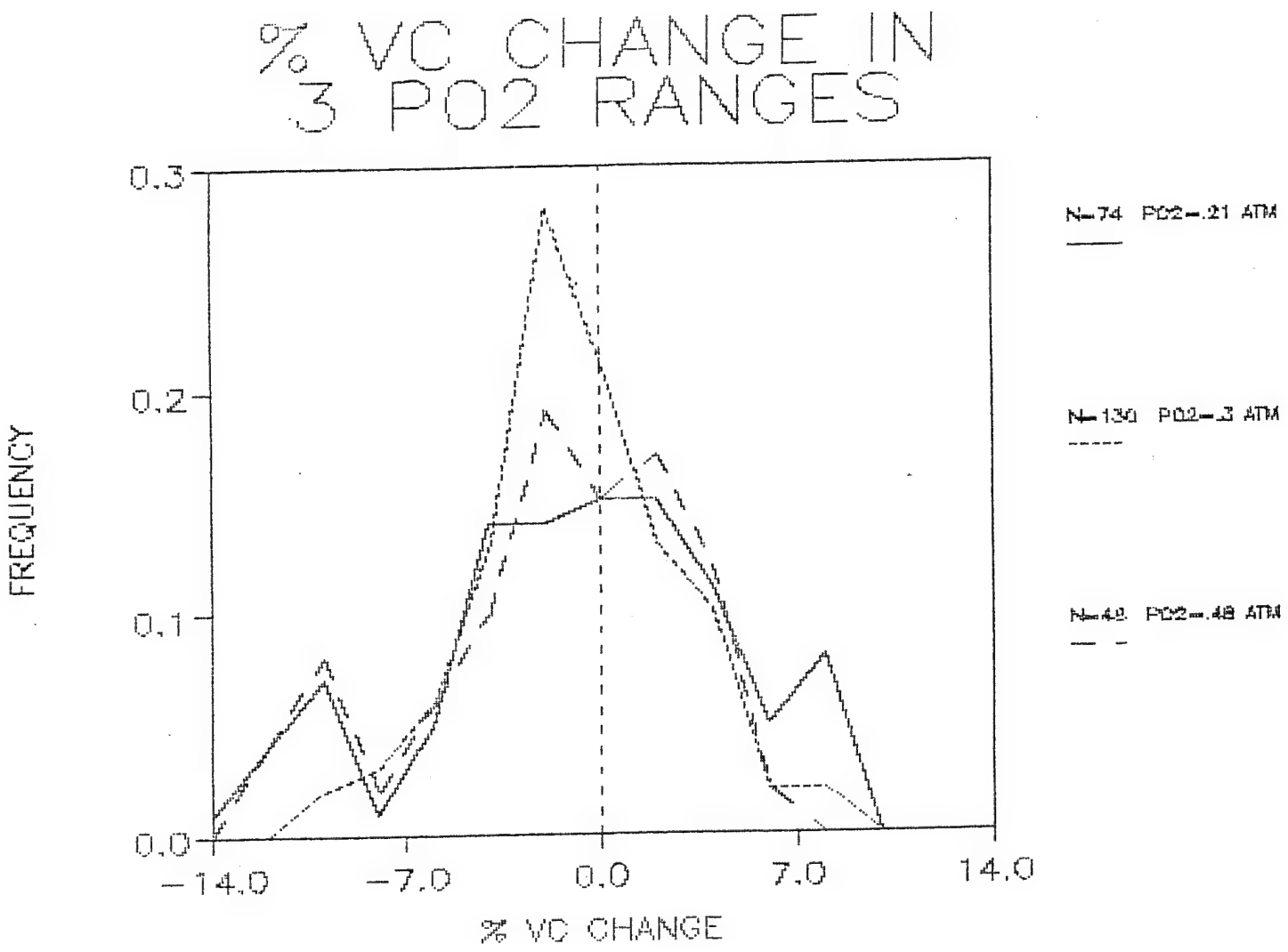


FIGURE 3. Mean % vital capacity change at low PIO2's.

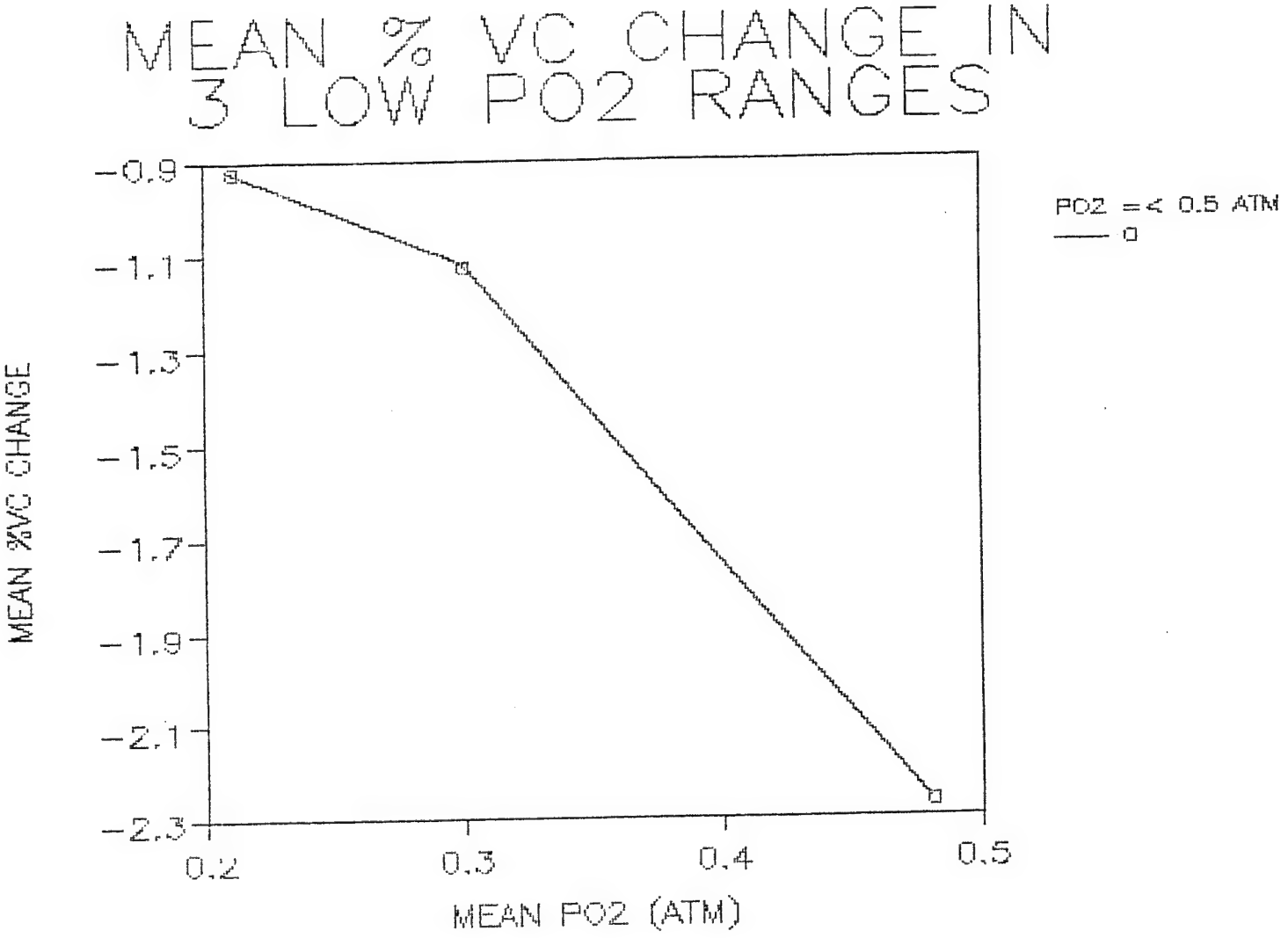


FIGURE 4. PIO2 profile for AIRSAT 4 dives reported by Eckenhoff and Vann (1985).

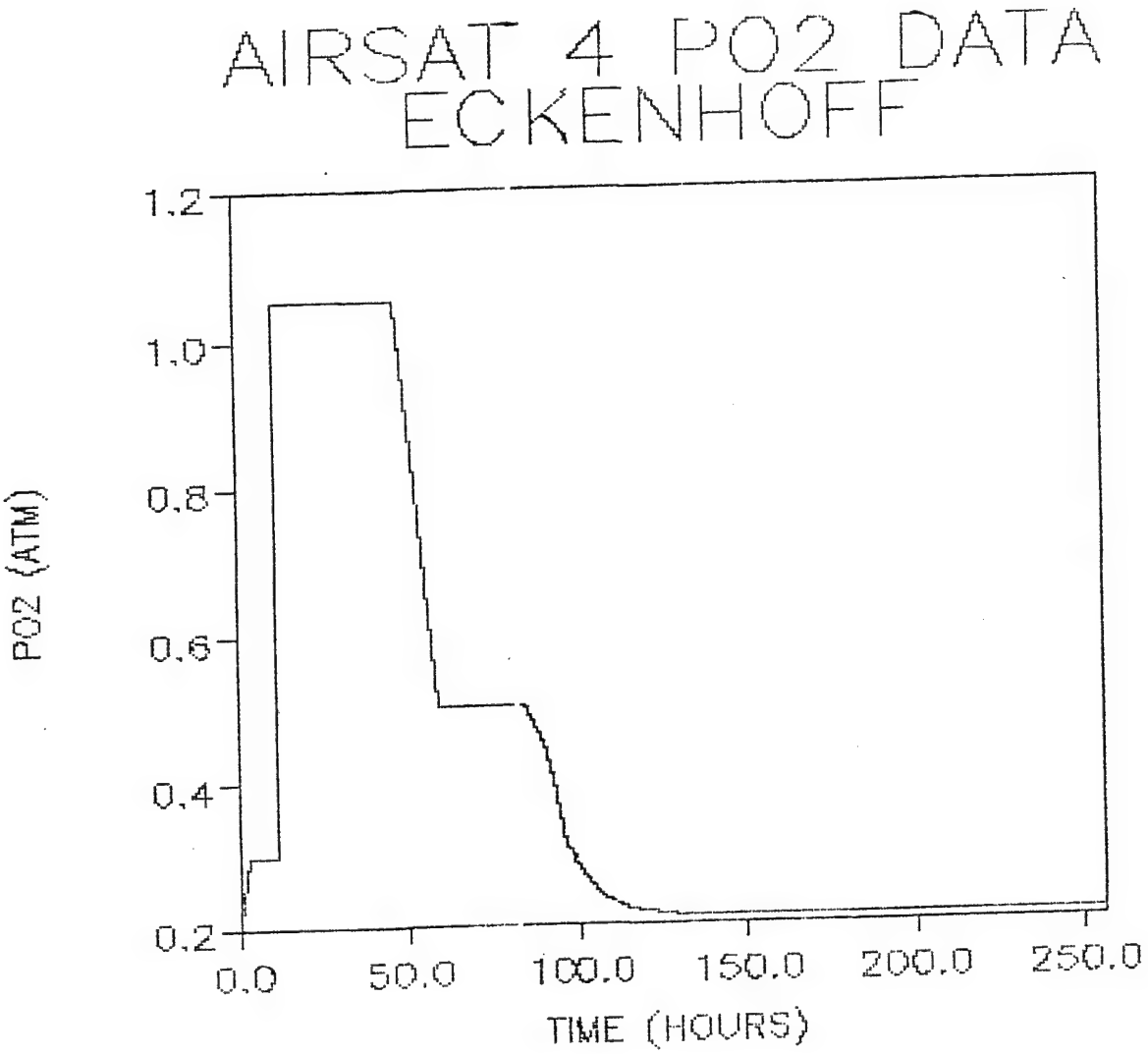


FIGURE 5. Percent change in vital capacity for 12 subjects during AIRSAT 4 dives (Fig. 5 from Harabin et al 1986).

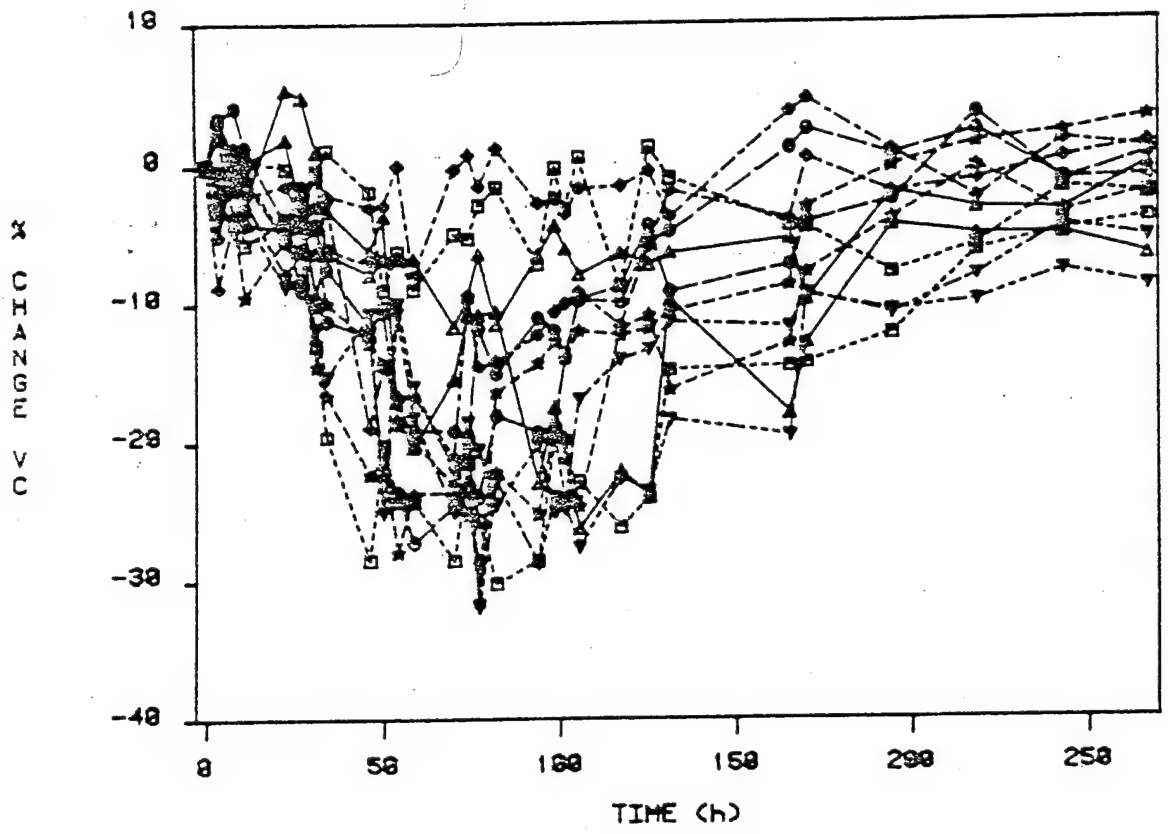


FIGURE 6. Predicted and mean experimental % changes in vital capacity for AIRSAT 4 divers (Model FR(2)-VC(2)).

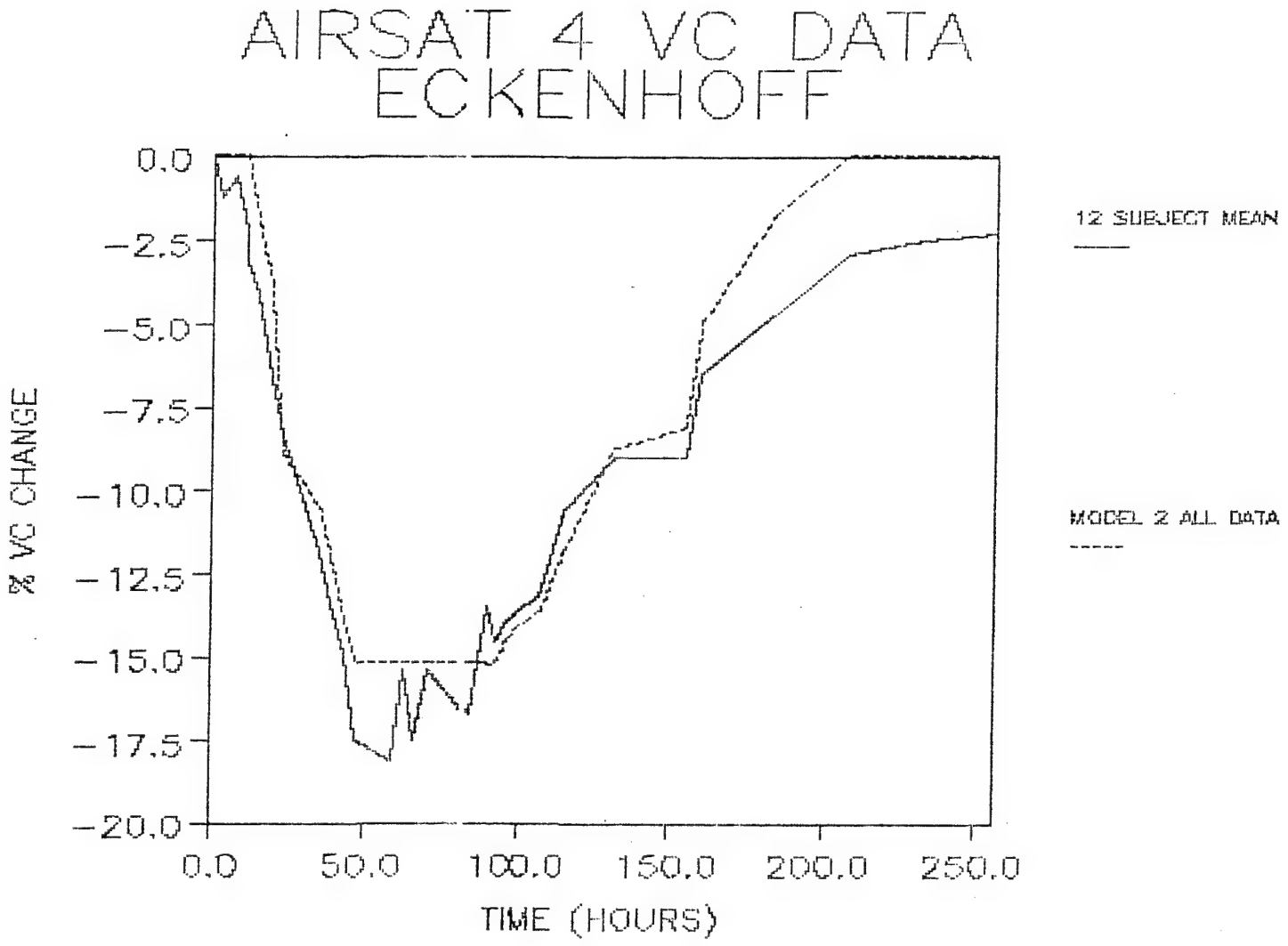


FIGURE 7. PIO2 profile for an oxygen dive at 20 fsw with an excursion to 40 fsw.

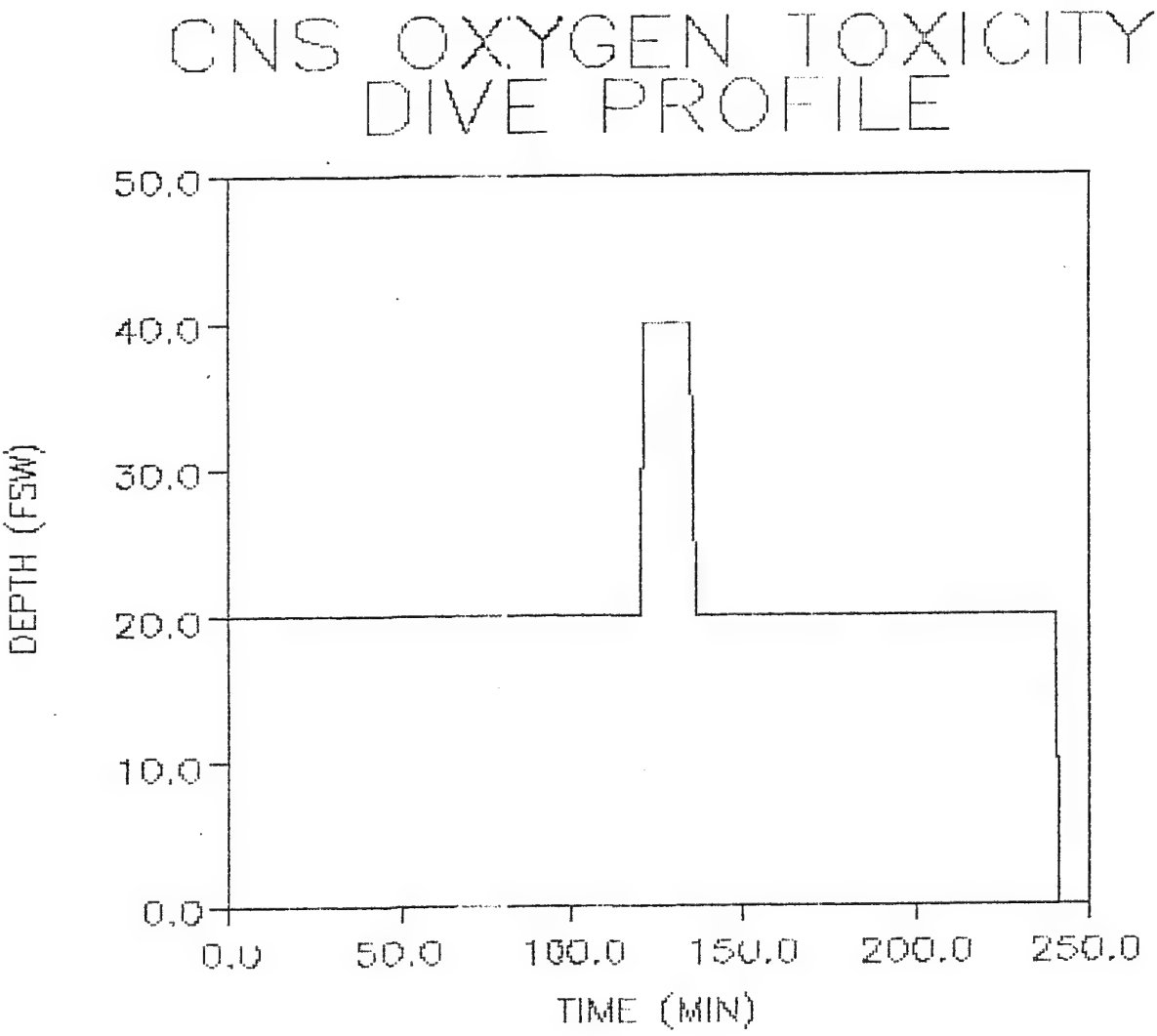
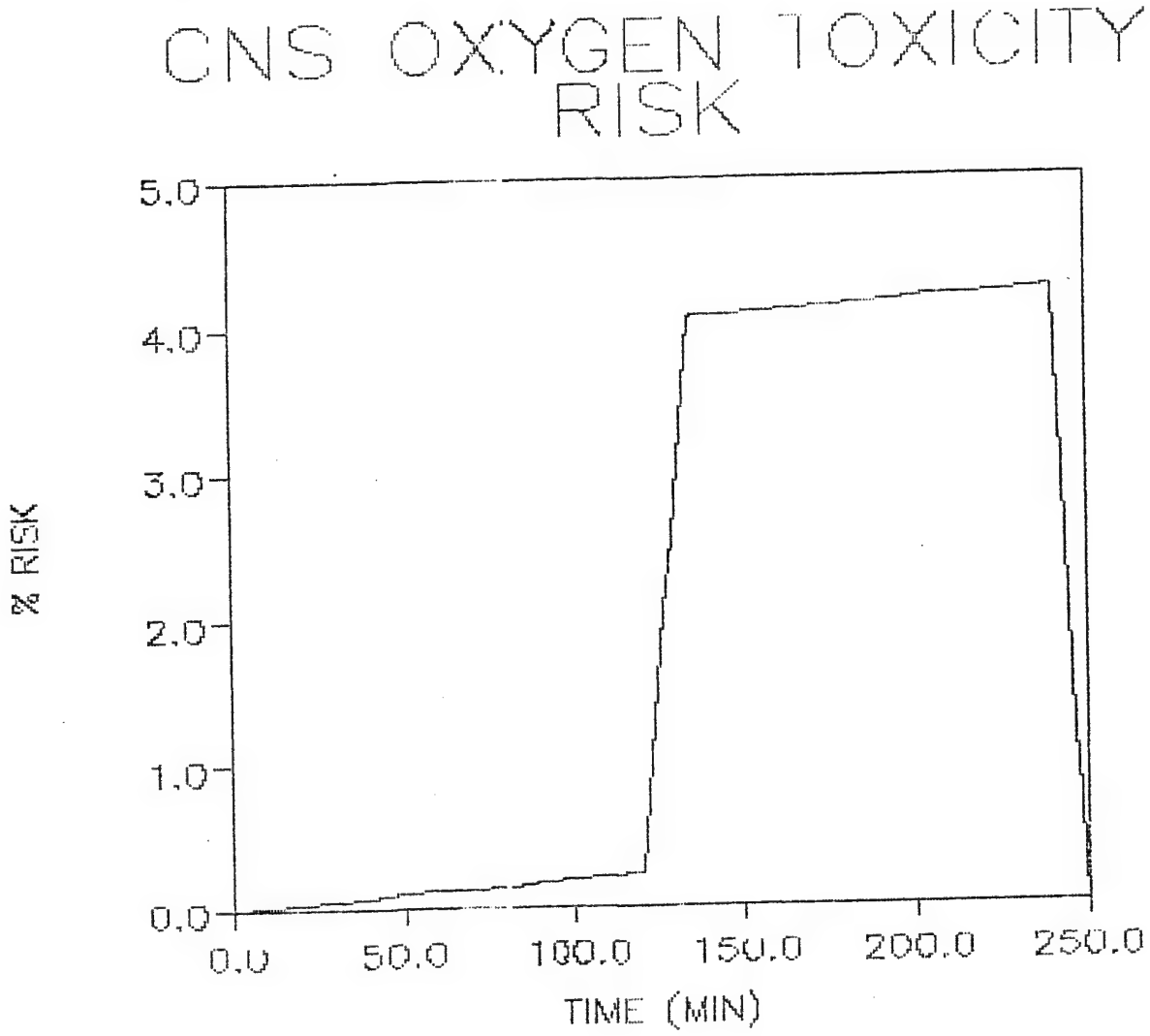


FIGURE 8. The development and resolution of CNS oxygen toxicity risk predicted for symptom category 2 and the dive profile of Fig. 7.



APPENDIX A - PARAMETER VALUES FOR PULMONARY TOXICITY MODELS

FR(1)-VC(1)
C1 = 0.24254555E-02
C2/C1 = 0.27838695E+00
SSE = 55948.39453125

FR(1)-VC(2)
C1 = 0.21004841E-01
C2/C1 = 0.40659472E+00
B1 = 0.10055144E+01
SSE = 31538.12695312

FR(2)-VC(1)
C1 = 0.92303315E-02
C2/C1 = 0.17013633E+00
C3 = 0.30700679E-03
SSE = 37213.92187500

FR(2)-VC(2)
C1 = 0.21297863E-01
C2/C1 = 0.41017273E+00
C3 =-0.28009774E-07
B1 = 0.10055192E+01
SSE = 31518.07421875

APPENDIX B - CEREBRAL PO2 AS A FUNCTION OF OXYGEN DEPTH

DEPTH	PIO2	PAO2	PVO2	DEPTH	PIO2	PAO2	PVO2
0.000	0.210	0.157	0.059	31.000	1.939	1.886	0.147
1.000	1.030	0.977	0.091	32.000	1.970	1.917	0.151
2.000	1.061	1.008	0.092	33.000	2.000	1.947	0.155
3.000	1.091	1.038	0.093	34.000	2.030	1.977	0.159
4.000	1.121	1.068	0.095	35.000	2.061	2.008	0.163
5.000	1.152	1.099	0.096	36.000	2.091	2.038	0.167
6.000	1.182	1.129	0.097	37.000	2.121	2.068	0.172
7.000	1.212	1.159	0.099	38.000	2.152	2.099	0.178
8.000	1.242	1.189	0.100	39.000	2.182	2.129	0.183
9.000	1.273	1.220	0.101	40.000	2.212	2.159	0.188
10.000	1.303	1.250	0.103	41.000	2.242	2.189	0.195
11.000	1.333	1.280	0.104	42.000	2.273	2.220	0.201
12.000	1.364	1.311	0.105	43.000	2.303	2.250	0.208
13.000	1.394	1.341	0.107	44.000	2.333	2.280	0.216
14.000	1.424	1.371	0.108	45.000	2.364	2.311	0.224
15.000	1.455	1.402	0.111	46.000	2.394	2.341	0.233
16.000	1.485	1.432	0.112	47.000	2.424	2.371	0.243
17.000	1.515	1.462	0.113	48.000	2.455	2.402	0.254
18.000	1.545	1.492	0.116	49.000	2.485	2.432	0.266
19.000	1.576	1.523	0.117	50.000	2.515	2.462	0.278
20.000	1.606	1.553	0.120	51.000	2.545	2.492	0.292
21.000	1.636	1.583	0.121	52.000	2.576	2.523	0.307
22.000	1.667	1.614	0.124	53.000	2.606	2.553	0.322
23.000	1.697	1.644	0.125	54.000	2.636	2.583	0.338
24.000	1.727	1.674	0.128	55.000	2.667	2.614	0.357
25.000	1.758	1.705	0.130	56.000	2.697	2.644	0.375
26.000	1.788	1.735	0.133	57.000	2.727	2.674	0.396
27.000	1.818	1.765	0.136	58.000	2.758	2.705	0.417
28.000	1.848	1.795	0.138	59.000	2.788	2.735	0.438
29.000	1.879	1.826	0.141	60.000	2.818	2.765	0.462
30.000	1.909	1.856	0.145				

25-MAY-88
15:52:40

APPENDIX C - PARAMETER VALUES AND RISK PREDICTION FOR CNS TOXICITY MODELS

SYMPTOM CATEGORY ONE

N 1 3 1.

1	2.0138952732	= B1
2	0.0000000000	
3	0.0117034214	= C1
4	0.1175345778	= C2/C1
5	-59.6790657043	= MAXIMUM LOG LIKELIHOOD

NUMBER OF SYMPTOMS = 11.
SYMPTOM CATEGORY = 1
NUMBER OF EXPOSURES = 773.
FRACTION WITH SYMPTOMS = 0.014
MODEL INDEPENDENT LIKELIHOOD = -9.8026247

	TIME AT INDICATED DEPTH AT FRACTIONAL RISK BELOW LINE							
DEPTH	0.01000	0.02000	0.03000	0.04000	0.05000	0.06000	0.07000	0.08000
10.00	-82.3	-165.5	-249.5	-334.3	-420.1	-506.7	-594.3	-682.9
15.00	-175.0	-351.8	-530.5	-710.9	-893.3	-1077.6	-1263.8	-1452.1
20.00	557.0	1119.7	1688.1	2262.5	2842.8	3429.3	4022.0	4621.2
25.00	96.4	193.7	292.1	391.4	491.8	593.3	695.9	799.5
30.00	45.1	90.6	136.7	183.2	230.1	277.6	325.6	374.1
35.00	26.9	54.0	81.5	109.2	137.2	165.5	194.1	223.1
40.00	17.4	34.9	52.6	70.5	88.6	106.9	125.4	144.1
45.00	11.6	23.2	35.0	46.9	59.0	71.1	83.4	95.9
50.00	7.7	15.4	23.2	31.1	39.1	47.2	55.3	63.6
55.00	5.1	10.3	15.6	20.8	26.2	31.6	37.1	42.6
60.00	3.6	7.2	10.8	14.5	18.2	21.9	25.7	29.6
DOSE(F)	0.01436	0.02886	0.04351	0.05831	0.07327	0.08838	0.10366	0.11910

	U.S. NAVY			
	OLD LIMITS		NEW LIMITS	
DEPTH	TIME	RISK	TIME	RISK
10.	240.	0.000	240.	0.000
15.	150.	0.000	240.	0.000
20.	110.	0.002	240.	0.004
25.	75.	0.008	240.	0.025
30.	45.	0.010	80.	0.018
35.	25.	0.009	25.	0.009
40.	10.	0.006	15.	0.009
50.	0.	0.006	10.	0.013

APPENDIX C - SYMPTOM CATEGORY TWO

25-MAY-88
15:21:51
N 1 3 2.

1	1.5738464594	= B1
2	16.1001243591	
3	0.0831923708	= C1
4	0.1192276925	= C2/C1
99	-173.59	= MAXIMUM LOG LIKELIHOOD

NUMBER OF SYMPTOMS = 44.
SYMPTOM CATEGORY = 2
NUMBER OF EXPOSURES = 773.
FRACTION WITH SYMPTOMS = 0.057
MODEL INDEPENDENT LIKELIHOOD = -14.3013067

TIME AT INDICATED DEPTH AT FRACTIONAL RISK BELOW LINE

DEPTH	0.01000	0.02000	0.03000	0.04000	0.05000	0.06000	0.07000	0.08000
10.00	-16.1	-32.3	-48.6	-65.2	-81.9	-98.8	-115.9	-133.2
15.00	-30.6	-61.5	-92.8	-124.3	-156.2	-188.5	-221.0	-254.0
20.00	523.2	1051.8	1585.7	2125.2	2670.4	3221.3	3778.1	4341.0
25.00	24.1	48.5	73.2	98.0	123.2	148.6	174.3	200.3
30.00	10.4	21.0	31.6	42.4	53.3	64.3	75.4	86.6
35.00	6.1	12.2	18.4	24.6	30.9	37.3	43.8	50.3
40.00	3.9	7.8	11.7	15.7	19.7	23.8	27.9	32.1
45.00	2.6	5.1	7.7	10.4	13.0	15.7	18.4	21.2
50.00	1.7	3.4	5.1	6.8	8.6	10.4	12.1	14.0
55.00	1.1	2.3	3.4	4.6	5.7	6.9	8.1	9.3
60.00	0.8	1.6	2.4	3.2	4.0	4.8	5.6	6.5

DOSE(F) 0.02216 0.04455 0.06716 0.09001 0.11310 0.13643 0.16002 0.18385

U.S. NAVY

	OLD LIMITS		NEW LIMITS	
DEPTH	TIME	RISK	TIME	RISK
10.	240.	0.000	240.	0.000
15.	150.	0.000	240.	0.000
20.	110.	0.002	240.	0.005
25.	75.	0.031	240.	0.095
30.	45.	0.042	80.	0.074
35.	25.	0.041	25.	0.041
40.	10.	0.026	15.	0.038
50.	0.	0.026	10.	0.058

25-MAY-88 APPENDIX C - SYMPTOM CATEGORY THREE
15:34:51

N 1 3 3.

1	1.7313301563	= B1
2	16.1001243591	
3	0.0840160698	= C1
4	0.1119670719	= C2/C1
5	-291.48	= MAXIMUM LOG LIKELIHOOD

NUMBER OF SYMPTOMS = 81.
SYMPTOM CATEGORY = 3
NUMBER OF EXPOSURES = 773.
FRACTION WITH SYMPTOMS = 0.105
MODEL INDEPENDENT LIKELIHOOD = -24.9281578

TIME AT INDICATED DEPTH AT FRACTIONAL RISK BELOW LINE

DEPTH	0.01000	0.02000	0.03000	0.04000	0.05000	0.06000	0.07000	0.08000
10.00	-23.3	-46.9	-70.8	-94.8	-119.1	-143.7	-168.6	-193.7
15.00	-151.3	-304.1	-458.4	-614.4	-772.0	-931.3	-1092.2	-1254.9
20.00	28.0	56.4	85.0	113.9	143.2	172.7	202.5	232.7
25.00	11.9	23.9	36.1	48.4	60.8	73.3	86.0	98.8
30.00	6.7	13.4	20.2	27.0	33.9	40.9	48.0	55.2
35.00	4.3	8.6	12.9	17.3	21.7	26.2	30.7	35.3
40.00	2.9	5.7	8.7	11.6	14.6	17.6	20.7	23.7
45.00	2.0	3.9	5.9	7.9	10.0	12.0	14.1	16.2
50.00	1.3	2.6	4.0	5.3	6.7	8.1	9.5	10.9
55.00	0.9	1.8	2.7	3.6	4.5	5.5	6.4	7.4
60.00	0.6	1.3	1.9	2.5	3.2	3.8	4.5	5.2

DOSE (F) 0.01831 0.03681 0.05549 0.07437 0.09345 0.11273 0.13221 0.15191

U.S. NAVY

	OLD LIMITS		NEW LIMITS	
DEPTH	TIME	RISK	TIME	RISK
10.	240.	0.000	240.	0.000
15.	150.	0.000	240.	0.000
20.	110.	0.039	240.	0.082
25.	75.	0.061	240.	0.183
30.	45.	0.066	80.	0.114
35.	25.	0.057	25.	0.057
40.	10.	0.035	15.	0.051
50.	0.	0.035	10.	0.074